PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P 824 PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00679	09.10.2003	10.10.2002

International Patent Classification (IPC) or both national classification and IPC
A61K38/17

Applicant
GASTROTECH PHARMA A/S

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.05.2004	14.10.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00679

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-88 as originally filed

Claims, Numbers

1-37 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32
	No:	Claims	33-37
Inventive step (IS)	Yes:	Claims	1-32
	No:	Claims	33-37
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: WO 01 56592 A (NOVO NORDISK AS) 9 August 2001 (2001-08-09)
   D2: EP-A-1 197 496 (KANGAWA KENJI) 17 April 2002 (2002-04-17)
   D3: H. ARIYASU ET AL.: "Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans." THE JOURNAL OF CINICAL ENDOCRINOLOGY & METABOLISM, vol. 86, no. 10, October 2001 (2001-10), pages 4753-4758, XP002223632
   D4: Y. DATE ET AL.: "The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats." GASTROENTEROLOGY, vol. 123, no. 4, 1 October 2002 (2002-10-01), pages 1120-1128, XP002223633

NOVELTY AND INVENTIVE STEP OF CLAIMS 33-37

2. **Claims 33-37 do not meet the requirements of Art. 33(2) and 33(3) PCT** for the reasons set out below.

2.1 **D1** [see claims 17-20 in conjunction with claims 1 and 7] discloses pharmaceutical compositions (i.e. compositions for use in medicine) comprising ghrelin of homologues thereof (or their salts) together with a pharmaceutical carrier. The compositions may comprise 0.1 to 500 mg of te active agent and they may be for oral, nasal, transdermal, pulmonal or parenteral administration.

Thus, **D1** destroys both the novelty and inventive step of the subject matter of the present claims 33-36.
[Note that except for the "first medical use" a product (e.g. a composition) is only defined by its components and not by the intended use].

2.2 **D2** [see e.g. p. 25, l. 20 to p. 31, l. 30 in conjunction with p. 72,, l. 41-45] discloses ghrelin analogs as specified in present claims 2-14 (or their salts) for use in medicine.

Hence, ~~D2 destroys~~ both the novelty and inventive ~~step of the subject matter of~~ the present claim 33-37.

NOVELTY AND INVENTIVE STEP OF CLAIMS 1-32

3. **Claims 1-32 meet the requirements of Art. 33(2) and 33(3) PCT** because their subject matter is new and inventive over the prior art documents cited in the search report (see below).

3.1 **Novelty:**
None of the prior art documents cited in the search report discloses the use of ghrelin or an analogue thereof for the preparation of a medicament for the treatment, prevention or stimulation of any of the different conditions specified in the independent main claim 1, **in gastrectomized individuals.**

3.2 **Inventive step:**
Ghrelin is a known GH secretagogue which increases release of GH, as well as food intake and body weight gain when administered centrally (intraventricularly in the CNS) or peripherally. It is also known that intraventricular administration of ghrelin activates NPY-producing neurons and increases the expression of NPY (neuropeptide Y), a peptide which is a potent stimulator of food intake (see e.g. **D3**: p. 4753, paragraphs 1-2 and **D4**: p. 1120, c. 2, l. 1-6).
On the other hand it has also been reported that the peripheral effect of ghrelin on GH secretion is profoundly diminished after vagotomy, whether subdiafragmic or gastric branched vagotomy. (See **D4**: p. 1123, c. 1, to p. 1124, c. 1, 1st paragraph).
[The vagus nerve is a cranial nerve innervating diafragmic and subdiafragmic organs, including the gastric mucosa. Gastrectomy invariably results in vagotomy of those vagal nerve fibres that innervate the stomach].

The subject matter of the present claims 1-32 is based on the finding that the administration of ghrelin or analogs thereof to gastrectomized animals (i.e. vagotomized animals) can nevertheless increase the expression of NPY. [This effect is supported by the experimental data of the application].
Hence contrary to the thought that the peripheral effects of ghrelin are abolished after vagotomy (gastrectomy), ghrelin can be used for increasing body weight and body fat in gastrectomized individuals.

The aforementioned finding is in no way suggested by the prior art cited in the

search report.

INDUSTRIAL APPLICABILITY:

6. claims 1-37 satisfy the criterion set forth in Art. 33(4) PCT because their subject matter is susceptible of industrial application.